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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,498	07/25/2003	David H. Farb	60601-CIP (60601)	3267

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EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 08/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,498	FARB ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 12-34* is/are pending in the application.

4a) Of the above claim(s) *3 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 12-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-3 and 12-33, and the species having NMDA receptors with identical NR1 subunits and different NR2 subunits, in the reply filed on 5/25/2006 is acknowledged. The traversal is on the ground(s) that searching all claims and species of the instant application would present a minimal search burden. This is has been fully considered and is not found persuasive. As set forth in the requirement for restriction mailed on 1/31/2006, inventions I and II are not disclosed as capable of use together, and thus represent unique methods with different process steps, reagents, and goals. Therefore, the groups of inventions I and II represent separate inventions. Furthermore, the two distinct species claimed in group I have different chemical structures, and therefore require separate searches.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-3 and 12-34 are currently pending. Due to the election of group I, claim 34 is withdrawn as non-elected subject matter. Furthermore, due to the election of the species having NMDA receptors with identical NR1 subunits and different NR2 subunits, claim 3 is withdrawn as non-elected subject matter.

3. Therefore, claims 1-2 and 12-33 are the subject of this office action.

Information Disclosure Statement

The information disclosure statements received on 8/24/2004, 12/6/2004, and 5/16/2005 have been fully considered.

Specification

The use of trademarks has been noted in this application. For example, the trademark QIAGEN appears on p. 63, line 3. Trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. Applicant is required to amend the specification wherever trademarks appear.

Claim Objections

1. The Examiner suggests the syntax of claim 1 can be improved by amending the claim to read on "A method for identifying a subunit-specific modulator....."

2. The Examiner suggests the syntax of claims 14, 16 and 17 can be improved by amending the phrase "α exon encoded protein" to "α-exon-encoded protein".

3. The Examiner suggests the syntax of claims 30 and 31 can be improved by amending the claims to recite "steroid-based" and "non-steroid-based", respectively.

4. The word "transmitter" is misspelled as "trasmitter" in claims 27 and 29.

5. Claim 24 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 12-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a subunit-specific modulator of the NMDA receptor using neurotransmitter recognition site ligands that are kainate, NMDA, glutamate, glycine, does not reasonably provide enablement for a method for identifying a subunit-specific modulator of the NMDA receptor using any other neurotransmitter recognition site ligand. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

In the instant case, the breadth of the claims is excessive because they are drawn to methods using any molecule or substance that could be considered a "neurotransmitter recognition site ligand", including ligands that are agonists or antagonists of any neurotransmitter recognition site, including non-NMDA recognition sites. The specification provides guidance and examples showing that kainate, glutamate, glycine, and NMDA are neurotransmitter recognition site ligands that recognize NMDA receptors, but does not teach any other neurotransmitter recognition site ligands. As written, the claims encompass methods using any potential molecule that could bind to any potential neurotransmitter recognition site. Von Bohlen *et al* (Neurotransmitters and Neuromodulators: Handbook of Receptors and Biological Effects, 2002, Wiley-VCH Verlang GmbH & Co. KGaA, Chapter 3, p. 40-115) reviews the activities of various neurotransmitters and neurotransmitter receptors. Von Bohlen teaches various antagonists and agonist or NMDA receptors (see p. 77, Table 3.7). Von Bohlen et al also teaches that acetylcholine is a ligand for muscarinic and nicotinic acid receptors (p. 44), but does not teach acetylcholine as a ligand for NMDA receptors. In general, von Bohlen *et al* teaches many diverse receptors, each with various ligands specific for an individual receptor or class of receptors. Thus, a person of ordinary skill in the art would not be able to predict which of many possible molecules or substances, other than kainate, glutamate, glycine, or NMDA, could act as neurotransmitter recognition site ligands, and thus be useful in the present

invention. For example, it would not be predictable to the skilled artisan to use acetylcholine as a neurotransmitter recognition site ligand in the method of the instant invention, because the skilled artisan would not be able to predict how contacting acetylcholine with an NMDA receptor would allow determination of subunit specificity. Furthermore, a skilled artisan would require further, undue experimentation to determine which molecules, other than kainate, glutamate, glycine, or NMDA, could bind specific NMDA receptor subunit combinations.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 1-2 and 12-33 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods utilizing neurotransmitter recognition site ligands, including agonists and antagonists. The claims do not require the neurotransmitter recognition site ligands of the instant invention to have any biological activity other than being an agonist or an antagonist of a neurotransmitter recognition site, nor any particular structure. The claims read on neurotransmitter recognition site ligands for NMDA receptor combinations, but also on neurotransmitter recognition site ligands for other receptors as well. Furthermore, the claimed neurotransmitter recognition site ligands can be molecules such as glycine or glutamate, or larger, more complex molecules, including antibodies specific for various receptor subunits. Thus, the claims are drawn to a genus of molecules that are not adequately described in the specification.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the neurotransmitter recognition site ligands are agonists or antagonists of any biological activity of any neurotransmitter receptor, including but not limited to different NMDA receptor subunit combinations. There is no identification of any particular biological activity to be stimulated or inhibited. Furthermore, although the specification

discloses glycine, glutamate, NMDA, and kainate as useful neurotransmitter recognition site ligands, the genus of ligands can encompass many types of molecules, and therefore these examples are not sufficient to adequately describe the genus. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus of molecules that are putatively capable of being an agonistic or antagonistic neurotransmitter recognition site ligand for any NMDA receptor subunit combination, or for any other type of neurotransmitter receptor.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-2 and 12-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites a method for identifying a subunit specific modulator of the NMDA receptor, wherein said method comprises assaying for receptor "activity" (part c). The claims do not recite a specific activity to be assessed, and a wide range of biological activities can be associated with a given receptor. For example, the ability to simply bind a ligand could be considered an "activity". Thus, the metes and bounds of the claim, as it relates to assessing receptor activity, cannot be determined.

2. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. As currently written, the claim is drawn to a method of providing a plurality of NMDA receptors and comparing the activity of one subunit to the activity of another subunit. Given the fact that more than one subunit may differ between or among NMDA receptors, the claims require a method step for determination of the subunit-specificity of a given modulator.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-2 and 26-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Park-Chung *et al* (*Mol. Pharmacol.* 1997, Vol 52, p. 1113-1123, cited in the information disclosure statement received on 8/23/2004). The claims of the instant invention are drawn to a method for identifying a subunit-specific modulator of the NDMA receptor, wherein said method comprises providing a plurality of NMDA receptors which differ in subunit identity, contacting the NMDA receptors with a candidate ligand, and assaying for reporter activity. The claims are further drawn to performing the assay in an oocyte expression system, and using ligands that are agonists or antagonists.

Park-Chung *et al* teaches a method of identifying subunit-specific modulators of the NMDA receptors in Xenopus laevis oocytes expressing $NR1_{100}$ and NR2A subunits (p. 1119, 1st column, 2nd paragraph), thus meeting the limitations of claims 1-2 and 26. Furthermore, Park-Chung *et al* disclose that the responses to NMDA receptor agonists (including NMDA, glutamate, and glycine) and an antagonist (APD, D-2-amino-5-phosphonovaleric acid – see p. 1119, 1st column, 3rd paragraph and Fig. 7) were modulated by both steroid modulators (pregnenalone sulfate and 3β5βs (3β-hydroxy-5β-pregnan-20-one sulfate), and non-steroid modulators (spermine and redox, see p. 1113), thus meeting the limitations of claims 27-33 of the instant invention.

2. Claims 1-2, 26-29, and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Durand *et al* (*Proc. Natl. Acad. Sci. USA.* 1992. Vol. 89, p. 9359-9363 – cited in the information disclosure statement received on 8/23/2004). The subject matter of the claims of the instant invention is described *supra*. Durand *et al* teaches modulation by spermine of NMDA receptors having NR1A and NR1B subunits that are expressed in oocytes (p. 9361, 2nd column, 2nd paragraph – p. 9362, 1st paragraph; see also Fig. 4), thus meeting the limitations of

claims 1-2 and 26 of the instant application. Durand *et al* also teaches NMDA receptor agonists, including the known non-steroidal neurotransmitters NMDA, glutamate, and glycine, and also antagonists (see Table 1), thus meeting the limitations of claims 27-29 and 31-33 of the instant invention.

3. Claims 1-2, 12-14, 20, 26-28, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Williams *et al* (*Mol. Pharmacol.* 1994. Vol. 45, p. 803-809 – cited in the information disclosure statement received on 8/23/2004). The subject matter of the claims of the instant invention is described *supra*. Claims 12-14 are further drawn to the claimed method wherein the plurality of NMDA receptors have identical NR1 subunits and differ in their NR2 subunits. Specifically, the NR1 subunits are selected from the subunits listed in claim 13, and the NR2 subunits are selected from the subunits listed in claim 20. Furthermore, claim 14 is drawn to an NR1 subunit containing an α-exon-encoded protein domain.

Williams *et al* disclose the modulatory effects by spermine of NMDA receptors with NR1 and NR2 subunits expressed in oocytes, thus meeting the limitations of claims 1-2 and 26-27 of the instant application. Specifically, Williams *et al* discloses modulatory effects of spermine on NMDA receptor complexes formed by identical NR1 subunits with different NR2 subunits. For example, Fig. 1 shows the response to spermine by receptors consisting of the NR1A subunit with either NR2A or NR2B, and NR1B with either NR2A or NR2B. Fig. 3 shows the response to spermine by receptors consisting of the NR1A subunit with either the NR2A, NR2B, or NR2C subunits. Thus, Williams *et al* meets the limitations of claim 12 of the instant application. Furthermore, NR1A is also known as $NR1_{011}$ and NR1B is also known as $NR1_{111}$, the latter of which is known to contain an α-exon (see p. 58 of instant specification), and therefore Williams *et al* also meets the limitations of claims 13-14 of the instant application. Finally, Williams *et al* teaches modulation of NMDA receptors by NMDA agonists such as NMDA, glutamate, and glycine (see Figs. 4 and 6), thus meeting the limitations of claims 27-28, 31, and 33.

4. Claims 1-2, 12-13, 15, 20, 26-29, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Daggett *et al* (US 5,849,895 – cited in the information disclosure statement received on 8/23/2004). The subject matter of the claims of the instant application is discussed *supra*. Claim 15 is further drawn to a chimeric isoform of an NR1 subunit.

Daggett *et al* discloses various NMDA receptor subunits (column 2, 1st full paragraph – 3rd paragraph; column 15, 1st full paragraph), including NMDR1A (NR1A or $NR1_{011}$), and NMDR2A-D (NR2A-D), and various methods for using these receptor subunits. Daggett *et al* also teach that the NMDA receptor subunits can be used in methods of screening compounds that modulate activity of NMDA receptors (column 16, 6th full paragraph – column 17, 4th full paragraph), including assays involving oocytes expressing various NMDA receptors. Furthermore, Daggett *et al* teaches expression of various NMDA receptors in oocytes, including identical NR1 subunits with different NR2 subunits (column 15, 1st full paragraph; Example 9; Table 1), and chimeric isoforms of NR1 receptors (Table 1, and Example 2, section D). Therefore, Daggett *et al* meets the limitations of claims 1-2, 12-13, 15, 20, and 26 of the instant application. Finally, Daggett *et al* teaches modulation of NMDA receptors by the agonists NMDA, glutamate, and glycine (Table 1), as well as subunit-specific antibodies (column 17, last paragraph - column 18, 4th paragraph). Therefore, Daggett *et al* also meets the limitations of claims 27-29, 31, and 33 of the instant application.

5. Claims 1-2, 12-15, 20, 26-28, 31-33 are rejected under 35 U.S.C. 102(a) as being anticipated by Masuko *et al* (*Mol. Pharmacol.* 1999. Vol. 55, p. 957-969 – cited in the information disclosure statement received on 8-24/2004). The subject matter of the claims of the instant application is discussed *supra*.

Masuko *et al* teaches various responses to various modulators by NR1 ($NR1_{011}$)/NR2 subunit-containing receptors, wherein both NR1 and NR2 subunits are mutated at various positions and are expressed in oocytes, thus meeting the limitations of claims 1-2 and 26. Masuko *et al* discloses responses of NR1/NR2 complexes to spermine (a non-steroidal modulator), NMDA receptor agonists (glutamate and glycine), and NMDA receptor antagonists (ifenprodil, see Figs. 1-8), therefore meeting the limitations of claims 27-28, 31, and 33. Specifically, Masuko *et al* teaches NMDA receptors containing identical NR1 subunits with different NR2 subunits (see Fig 4 and p. 961, 1st column, 3rd paragraph), and receptor complexes containing $NR1_{011}$ (NR1A) and NR2B (see Fig 4), thus meeting the limitations of claims 12-13 and 20 of the instant application. Furthermore, Masuko *et al* teaches NR1 subunits containing an α-exon (see Fig 5), which can be interpreted as a chimeric NR1 protein, thus meeting the limitations of claims 14 and 15.

6. Claims 1-2, 12-15, 20, 26-28, 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Traynelis *et al* (*J. Neurosci.* 1998. Vol. 18, p. 6163-6175 – cited in the information disclosure statement received on 8/23/2004). The subject matter of the claims of the instant application is discussed *supra*.

Traynelis *et al* disclose modulation by spermine and zinc of NR1/NR2 receptor subunits expressed in oocytes, thus meeting the limitations of claims 1-2 and 26 of the instant application. Traynelis *et al* also discloses NMDA receptors containing an identical NR1 subunit with different NR2 subunits, (see Fig. 2B), subunits with NR1A ($NR1_{011}$, see Fig 1), and further discloses NR1A subunits containing an α-exon (Figs 1-2), which can be considered a chimeric isoform of NR1A. Therefore, Traynelis *et al* also meets the limitations of claims 12-15 and 20 of the instant application. Finally, Traynelis *et al* teaches stimulation with agonists such as glutamate and glycine, meeting the limitations of claims 27-28, 31, and 33 of the instant application.

7. Claims 1-2 12-13, 22, 24-28, 31, and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuner *et al* (*J. Neurosci.* 1996. Vol. 16, p. 3549-3558). The subject matter of the claims of the instant application is discussed *supra*. Claims 20-25 are further drawn to NDMA receptor complexes containing an NR2 subunit that is NR2A-D, and wherein the NR2 receptor subunit is chimeric and contains various amino acid residues of NR2B, or is an isoform point-mutant.

Kuner *et al* teach co-expression of NR1/NR2 subunits in oocytes and modulation of NMDA receptor response by glutamate or glycine (see Materials and Methods, p. 3550, 1st column, 3rd and 5th paragraphs). Specifically, Kuner *et al* discloses co-expression of NR1A ($NR1_{011}$) with different NR2 isoforms (for example, see Figs. 1-2), thus meeting the limitations of claims 1-2, 12-13, and 26-28, 31, and 33 of the instant application. Kuner *et al* also discloses various NR2 isoforms, including chimeric isoforms of NR2C wherein various regions of NR2B have replaced various regions of NR2C. These chimeric isoforms include NR2C chimeras containing the M1-M4 regions of NR2B, which comprise amino acids 534-879 (see Fig. 5 for schematic diagram, and Table 1 for listing of NR2 chimeras expressed with NR1A. Note: chimera M14 in Table 1 represents a NR2C chimera containing the M1-M4 regions of NR2B). Additinally, Kuner *et al* teaches various point mutants of NR2C (see Table 1). Therefore, Kuner *et al* meets the limitations of claims 20-22 and 24-25 of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daggett *et al* in view of Masuko *et al*. The subject matter of the claims of the instant application is discussed supra. Claims 18-19 are further drawn to RN1 subunits comprising various point mutations, including mutations at residues 182, 193, 202, 233, or 252 or $NR1_{011}$ (NR1A), and specifically R182A, K193A, K202A, R233A, and R252A mutations of NR1A.

The disclosure of Daggett *et al*, as it pertains to methods of using various NMDA receptor subunits to identify modulators of NMDA receptors, is discussed supra. Daggett *et al* is silent regarding any of the NR1 mutations claimed in the instant invention. Masuko *et al* teaches various NR1A mutants, and methods for using NR1A mutants to identify important residues/regions for the NMDA response to agonists or antagonists. Although Masuko et al does not specifically disclose mutation of amino acids 182, 193, 202, 233, or 252 of NR1A, various other mutants are disclosed, including mutants at postions 181, 192, 251, and 253 (see Fig 1).

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was conceived, mutate other residues of NR1. The motivation to do so comes from Daggett *et al*, which teaches that various NR1/NR2 subunit combinations can be used to screen for compounds with NMDA modulatory properties, and Masuko *et al*, which teach methods of determining the role of various amino acid residues of NR1A in responding to various agonists/antagonists. The skilled artisan would recognize the importance of determining the effect of specific receptor mutations on the response to various pharmacological substances, and would thus be motivated to create different NR1A subunit mutants, and screen them for receptor activity. Such methods would be within the skilled artisan's abilities, as Daggett *et al* and Masuko *et al* both teach methods of expressing various subunits and assessing the response of these expressed subunits to various agonists/antagonists, and various methods of

creating mutants, such as alanine-scanning mutagenesis, are well-known in the art. Therefore, by following the combined teachings of Daggett *et al* and Masuko *et al*, one of ordinary skill in the art would have both the motivation, and a reasonable expectation of success, in creating and NR1A mutants that are commensurate in scope with the claims of the instant invention, and then using them in a method that is commensurate in scope with the claims of the instant invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 26-29, and 32-33 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 5-10 of U.S. Patent No. 6,623,933. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-2 of the instant application, as well as claim 1 of the '933 patent, are drawn to a method of identifying subunit-specific modulators of the NMDA receptor, wherein said method comprises providing a plurality of NMDA receptors which differ in subunit identity, contacting the subunits in the presence of a candidate modulator, and assaying for receptor activity. Claim 26 of the instant application and claim 5 of the '933 patent both recite the claimed assay in an oocyte expression system. Finally, claims 27-29 and 32-33 of the instant application and claims 6-10 of the '933 patent both recite neurotransmitter recognition site

ligand agonists (including NMDA, glutamate, and glycine) and antagonists, and candidate molecules that are known neuromodulators or selected from a library of small molecules.

Therefore, due to the similarity of the methods of the instant application and the '933 patent, including methods comprising a plurality of NMDA receptors differing in subunit identity, a person of ordinary skill in the art would find it obvious to practice the methods of claims 1-2, 26-29, and 32-33 of the instant invention by following the disclosure of claims 1 and 5-10 of the '933 patent.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

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